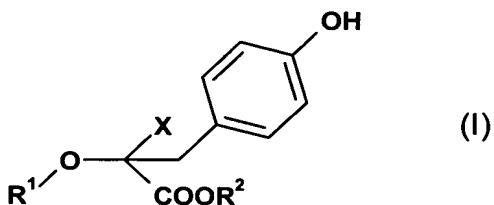


**Process for the Production of  $\alpha$ -alkoxy/hydroxy- $\beta$ -(p-hydroxyphenyl) Propionic Acid Derivatives**

The present invention is directed at a process for the production of  $\alpha$ -alkoxy/hydroxy- $\beta$ -(p-hydroxyphenyl) propionic acid derivatives. In particular the invention concerns the production of compounds having the general formula (I)



10 Compounds having formula (I), in particular where  $X = H$ , are important intermediates for the production of biologically active compounds. For example, so-called peroxisome proliferator-activating receptor agonists (ragaglitazar) have a corresponding partial structure (J. Med. Chem. 2003, 46, 1306-17; Organic Process Research & Development 2003, 7, 82-88).

15 A number of syntheses have become known for the production of the compounds under consideration. For example, WO0140159 suggests inter alia a multistage synthesis route 20 in which the corresponding condensation product is generated from the corresponding methoxybenzaldehyde and ethoxyacetic acid ester under basic conditions and the product thus obtained is eliminated to the conjugated system. Hydrogenation is followed by conversion to the 25 corresponding acid, a classic resolution of racemates, elimination of the methyl protective group and finally another esterification. The total yield appears to be modest.

S. Ebdrup et al. propose a Wittig-Horner strategy starting

from 4-(benzyloxy)benzaldehyde and ethyl-2-(diethylphosphinyl)-2-ethoxyacetate.

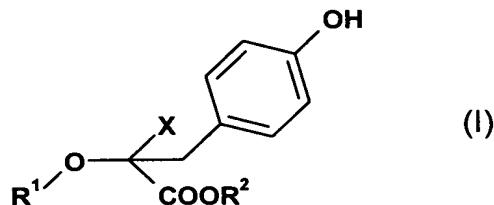
In all cases production of the racemic compound requires a complex synthesis with many stages and expensive reagents before resolution into the enantiomers. As the costs and the environmental loading due to the resolution of the racemates, which occurs late on in the synthesis, require production of at least twice the amount of racemate, a simple and environmentally friendly synthesis of the compounds having formula (I) is important.

The object of the present invention was therefore to provide another production method for the compounds having the general formula (I). The method should be able to be used on an industrial scale very successfully from an economic and ecological perspective, i.e. it should be robust, start from as favourable starting materials as possible and involve few stages.

This and other objects not mentioned in any more detail but obviously arising from the prior art are achieved by a process with the features of the present claim 1. Preferred embodiments of the process according to the invention are described in the subordinate claims depending on claim 1.

In a process for the production of compounds having the general formula (I)

25



wherein

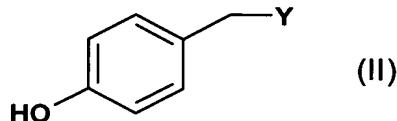
X = H or a group having an electron-attracting effect,

R<sup>1</sup> or R<sup>2</sup> are mutually independently H, (C<sub>1</sub>-C<sub>8</sub>) alkyl, (C<sub>3</sub>-C<sub>8</sub>)

30 cycloalkyl, (C<sub>1</sub>-C<sub>8</sub>) alkyl (C<sub>3</sub>-C<sub>8</sub>) cycloalkyl, (C<sub>3</sub>-C<sub>8</sub>)

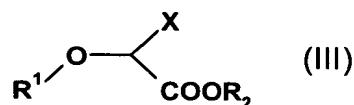
cycloalkyl ((C<sub>1</sub>-C<sub>8</sub>) alkyl)<sub>1-3</sub>, (C<sub>2</sub>-C<sub>8</sub>) alkenyl, (C<sub>2</sub>-C<sub>8</sub>) alkynyl, (C<sub>6</sub>-C<sub>18</sub>) aryl, (C<sub>7</sub>-C<sub>19</sub>) aralkyl radical, (C<sub>6</sub>-C<sub>18</sub>) aryl ((C<sub>1</sub>-C<sub>8</sub>) alkyl)<sub>1-3</sub>,

5 the stated object is achieved quite surprisingly, but no less successfully for that and especially advantageously according to the invention, by reacting compounds having the general formula (II)



10 wherein

Y represents a nucleofugal leaving group,  
with compounds having the general formula (III)



15 wherein

R1, R2 and X can assume the meaning stated above,  
under basic conditions.

Under the cited reaction conditions, compounds having  
formula (II) react so well with the nucleophile obtainable  
20 from (III) that the desired intermediates, such as e.g.  $\alpha$ -  
alkoxy- $\beta$ -(p-hydroxyphenyl) propionic acid can be obtained  
in up to a 90% yield. It is likely that the yield could be  
increased still further by additional process optimisation.  
According to the invention this process is started from  
25 compounds that are available commercially.

For access to compounds having formula (III) by synthesis,  
reference is made to the following literature: Monatshefte  
Chemie 1965, 1677-1689; J. Chem. Soc., Perkin Trans. 1:  
Org. Bioorg. Chem. 1976, 23, 2483-4; Synthesis 1975, 4,

269-70; J. Chem. Soc., 1933, 1628; Chem. Ber. 1991, 8, 1853-1863; JACS 1988, 110, 209-213.

In selecting groups X and Y, the person skilled in the art has a free choice in principle, provided that they are compatible with the reaction. Hydrogen and electron-attracting groups are suitable for X. The introduction of electron-attracting groups further increases the acidity of (III), which makes it possible to use milder bases. As groups X the person skilled in the art can preferably choose examples that afterwards allow a hydrogen radical to be introduced at the  $\alpha$ -carbon atom as easily as possible. This can be done by a substitution or reduction reaction or elegantly also by a decarboxylation and/or decarbonylation reaction. In the latter context the use of corresponding 1,3-dicarboxyl or 1,3-dicarbonyl derivatives is particularly worthy of mention. It is therefore particularly preferred if X is a radical selected from the group containing  $\text{CCl}_3$ , CN,  $\text{COOR}_1$ ,  $\text{COR}_1$ ,  $\text{COCOOR}_1$ . The radical Y is a nucleofugal leaving group. This type of radical is familiar to the person skilled in the art (Organikum, VEB Deutscher Verlag, 1986, 16<sup>th</sup> edition p. 170 ff). Mechanistic analyses suggest that the reaction proceeds via p-quinone methide. It is of course also conceivable, however, that the reaction proceeds in the manner of  $\text{SN}_1$  via substitution of the benzyl cation or in the manner of  $\text{SN}_2$  via a direct substitution of the leaving group Y. The mechanistic course of the reaction will be governed by the leaving group Y and the reaction conditions used. The use of radicals Y selected from the group containing OH, Cl, Br, OTs, OAc,  $\text{OCOCF}_3$ , OMs is conceivable.

With regard to the radicals  $\text{R}^1$  and  $\text{R}^2$  the person skilled in the art does not need to observe any restrictive boundary conditions. As stated, they should be inert in respect of the reaction and be as inexpensive as possible. In this context H or ( $\text{C}_1\text{-C}_8$ ) alkyl are therefore preferred for both

radicals. Emphasis should be given to the use of the methyl or ethyl radical for R<sup>1</sup> and/or R<sup>2</sup>.

The person skilled in the art also has a free choice of the solvent to be used. It should be as inexpensive as

5 possible, again be inert under the reaction conditions and furthermore should allow the reaction to proceed in the best possible way. Organic solvents having a aprotic dipolar character are preferred, such as e.g. NMP, DMPU, DMF, DMSO, sulfolane. However, (C<sub>1</sub>-C<sub>8</sub>) alkyl alcohols can 10 also be used for the reaction, such as e.g. tert.-amyl alcohol, ethanol, propanol, tert.-butanol, isopropanol, n- or sec-butanol. The use of polar aprotic solvents such as THF, MTBE, DME or CH<sub>3</sub>CN or any mixtures of the cited solvents also seems conceivable.

15 The use of the base is governed by the nature of the deprotonating substrate (III) to be used. For example, for compounds (III) where X = H stronger bases such as LDA, NaH, KH, LiHMDS, KHMDS or NaHMDS must be used. As the 20 electron-attracting effect of the radical X increases, the strength of the base to be used can be reduced more and more, so that (C<sub>1</sub>-C<sub>8</sub>) alkyl alkoxides (preferably dissolved or suspended in (C<sub>1</sub>-C<sub>8</sub>) alkyl alcohols) such as NaOMe, NaOEt, KOtBu etc., or stronger N bases such as Et<sub>3</sub>N, DBU, DBN, TMG, pentamethyl guanidine, diisopropyl ethylamine, 25 phosphazenes (R.Schwesinger, H.Schlemper, Angew.Chem.99, 1212 (1987); R.Schwesinger, Nachr. Chem. Tech. Lab. 38, 1214 (1990); H.Schlemper, University of Freiburg dissertation, 1990; R.Schwesinger, Chimia 39, 269 (1985); T.Pietzonka, D.Seebach, Chem. Ber. 124, 1837 (1990); H.- 30 J.Gais, J.Vollhardt, .Krüger, Angew.Chem.100,1108 (1988); M.Fletschinger, B.Zipperer, H.Fritz, H.Prinzbach, Tetrahedron Lett. 28, 2517 (1987)) can be used for more CH-acid compounds (III).

35 The reaction is preferably performed by introducing the base into the respective solvent and adding the compound (III). The substrate (II) is then added to the

mixture and reacted at temperatures of -30°C to 120°C, preferably -20°C to 100°C, most particularly preferably -20°C to 80°C. The chosen sequence of addition can also be the other way round, however. The product is isolated by a method known to the person skilled in the art, e.g. after separating the salts by evaporating the filtrate in vacuo (-> ester) or after saponification, acidification preferably by crystallisation of the corresponding acid.

Further processing can then take place by methods familiar to the person skilled in the art (see p. 1, line 13).

Methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert.-butyl, pentyl, hexyl, heptyl or octyl together with all bonding isomers can be regarded as (C<sub>1</sub>-C<sub>8</sub>) alkyl.

(C<sub>2</sub>-C<sub>8</sub>) alkenyl is understood to be a (C<sub>1</sub>-C<sub>8</sub>) alkyl radical as set out above (with the exception of methyl), that displays at least a double bond.

(C<sub>2</sub>-C<sub>8</sub>) alkynyl is understood to be a (C<sub>1</sub>-C<sub>8</sub>) alkyl radical as set out above (with the exception of methyl), that displays at least a triple bond.

(C<sub>3</sub>-C<sub>8</sub>) cycloalkyl is understood to be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl radicals, etc. These can display radicals containing N or O atoms in the ring, such as e.g. 1-, 2-, 3-, 4-piperidyl, 1-, 2-, 3-pyrrolidinyl, 2-, 3-tetrahydrofuryl, 2-, 3-, 4-morpholinyl.

A (C<sub>6</sub>-C<sub>18</sub>) aryl radical is understood to be an aromatic radical having 6 to 18 C atoms. These include in particular compounds such as phenyl, naphthyl, anthryl, phenanthryl and biphenyl radicals.

A (C<sub>7</sub>-C<sub>19</sub>) aralkyl radical is a (C<sub>6</sub>-C<sub>18</sub>) aryl radical bonded to the molecule via a (C<sub>1</sub>-C<sub>8</sub>) alkyl radical.

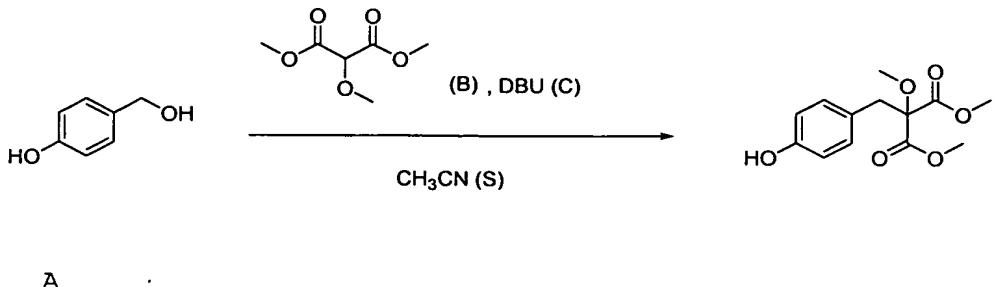
Within the meaning of the invention the term enantiomer-concentrated is understood to refer to the proportion of an enantiomer in the mixture with its optical antipode in a range between >50 % and <100 %.

- 5 The chiral structures shown refer to all possible diastereomers and enantiomers (R-, S-) as well as to mixtures thereof and the racemate.

The cited references are to be regarded as being included in the disclosure of this invention.

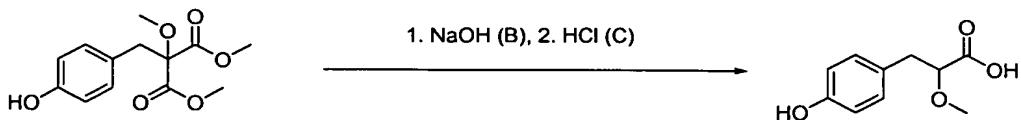
Examples:

Example 1:



5 4-Hydroxybenzyl alcohol (1 g, 0.0081 mol, A) was suspended in acetonitrile (2 ml), to which 2-methoxydimethyl malonate (0.0161 mol, 2.61 g, 2.2 ml, B) and DBU (0.0041 mol, 0.62 g, 0.61 ml, C) were added. The suspension was refluxed for 3 hours. The reaction mixture was cooled and the  
 10 solvent evaporated. 20 ml water were added to the residue and the emulsion obtained was extracted with 3 x 20 ml ethyl acetate. The collected organic phases were dried over MgSO<sub>4</sub>. After removal of the solvent by distillation a yellowish oil (1.92 g, 88 %) was obtained, which  
 15 crystallised after being left to stand.

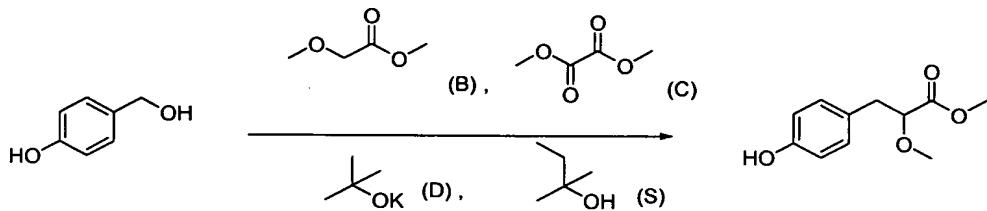
Example 2:



20 2-(4-Hydroxybenzyl)-2-methoxydimethyl malonate (1 g, 0.0037 mol) was added to a solution of NaOH (0.0112 mol, 0.45 g) in water (4 ml) and the reaction mixture was stirred for 3 hours at room temperature. 13 ml of concentrated HCl were then slowly added to the resulting solution and the emulsion was extracted with 3 x 10 ml  
 25 ethyl acetate. The water phase was evaporated to dryness. The resulting white solid was dissolved in dilute HCl (5 ml

water and 1 ml concentrated HCl) and refluxed for 16 hours. After cooling, the solution was extracted with 3 x 10 ml methyl isobutyl ketone. The combined organic phases were dried over MgSO<sub>4</sub>. After removal of the solvent by distillation an orange-coloured oil (0.5 g, 69 %) was obtained, which gradually crystallised after being left to stand.

Example 3:



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Potassium tert.-butylate (5.387 g, 0.0480 mol) was suspended in 2-methyl-2-butanol (30 ml). Then methoxymethyl acetate (0.0480 mol, 5.000 g, 4.8 ml) and dimethyl oxalate (0.0480 mol, 5.668 g) were added. The suspension was stirred for 1 hour at room temperature under an N<sub>2</sub> atmosphere. 4-Hydroxybenzyl alcohol (0.0408 mol, 5.065 g) was added in one portion and the reaction mixture refluxed for 30 minutes (oil bath 120 °C). The thick suspension was cooled in an ice bath to 5 °C. 100 ml MTBE were added. The insoluble solid was filtered off and the filter cake washed with 30 ml MTBE. The filtrate was concentrated to dry it and the residue dried to constant weight in an oil pump vacuum. After evaporation and drying, α-methoxy-β-(p-hydroxyphenyl) methyl propionate was obtained as an orange-coloured oil (8.0 g, 79 %). The methyl ester group was hydrolysed under the same conditions as in Example 2.